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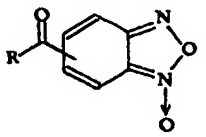
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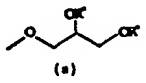
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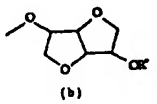
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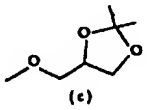
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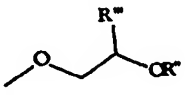
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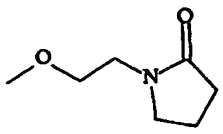
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(57) Abstract

The invention discloses a novel compound of the benzofuroxan series used for cardiovascular disorders represented by general formula (I) and pharmaceutically acceptable salts thereof wherein: R is –O–(CH_2)n–X–R'; n = 1 to 6; X is –NHC(O)–, oxygen or null; R' is lower alkyl (C_1–C_8), aromatic, heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two heteroatoms such as nitrogen or oxygen wherein substitution is with lower alkyl; or R is selected from (a), (b), (c), (d) or (e) wherein R'' is hydrogen, nitro, lower alkyl or –C(O)–R''' wherein R''' is hydrogen, lower alkyl or aryl. The invention also discloses process for the preparation of compounds of general formula (I). The invention also discloses the use of the compounds of general formula (I) as defined above, as NO donors and/or in coronary heart diseases, and pharmaceutical compositions containing compounds of general formula (I) as active ingredients. The invention also discloses a method of treatment of mammal, including man, of coronary heart disease by administration of an effective amount of a compound of formula (I) as defined above.

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BENZOFUROXAN DERIVATIVES AND THEIR USE IN TREATING ANGINA PECTORIS

FIELD OF THE INVENTION

This invention relates to novel compounds of benzofuroxan series and to their use in therapeutics. In particular the invention concerns novel benzofuroxan derivatives, method for their preparation, pharmaceutical compositions containing these compounds, their use as tolerance resistant nitric oxide donors in treatment of angina pectoris.

BACKGROUND OF THE INVENTION

After the discovery of endothelium-derived relaxing factor (EDRF) by Furchgott et al (1980), and the elucidation of the biochemistry of EDRF by a number of laboratories (Ignarro, 1989; Vane et al, 1990; Bassenge et al, 1988; and Vanhoutte, 1989), it is now widely accepted that EDRF is the endogenous nitrovasodilator, nitric oxide (NO) donor. The organic nitrates and related compounds owe their pharmacological action to the release of nitric oxide (NO) and these compounds are collectively called nitrovasodilators. NO stimulates the guanylate cyclase enzyme in vascular smooth muscle cells resulting in increased levels of cyclic GMP. This leads to dephosphorylation of myosin light chain which results in relaxation of smooth muscles (Murad, 1986). NO is known to be involved in a number of bio-regulatory processes like, vasodilatation, platelet deaggregation, vascular smooth muscle proliferation, etc.

Organic nitrates are used in prophylaxis, treatment and management of patients with angina pectoris. These are also useful in congestive heart failure associated with acute myocardial infarction, hypertension associated with surgica l procedures and to

produce controlled hypotension during surgical procedures. Among organic nitrates, nitroglycerine (sublingual) which is currently in use, is the drug of choice for immediate relief of anginal symptoms. Prophylactic treatment of stable angina pectoris involves the use of one or more drugs such as long acting nitrates like isosorbide dinitrate, a beta-blocker and/or a calcium channel antagonist, particularly in patients likely to experience coronary spasm. In some cases this triple therapy satisfactorily control angina. They are quite effective in the treatment of these conditions when used intermittently.

Frequently repeated use of nitrates result in decrease in their pharmacological effects, a phenomenon well recognized as nitrate tolerance. The mechanism of tolerance is not well defined. As early as 1973, Needleman and Johnson (1973) have reported that tolerance to nitroglycerine could occur in isolated rabbit arteries. It was hypothesized by them that depletion of sulphydryl groups was associated with the development of tolerance to nitroglycerine. This is a major problem in the clinical use of organic nitrates (Frampton et al, 1992). Currently, the development of tolerance is reduced by the use of intermittent dosing schedule with a nitrate-free interval of 10 - 12 hrs. However, this intermittent use is associated with decreased exercise tolerance during the last part of nitrate-free interval. This suggests possibility of increased frequency of or severity of angina during nitrate-free interval. The importance of development of tolerance has increased as these drugs are used more commonly in various dosage forms like oral, transdermal, and intravenous preparations and even as sustained-release preparations. Several indirect indices like exercise duration, systemic blood pressure, pulmonary artery pressures and pulmonary artery wedge pressure has been used to assess tolerance to organic nitrates. However, it is not clear

whether decreased response to nitrates is due to tolerance of the vascular smooth muscle cells or changes in regulatory factors like activation of neurohumoral factors or fluid retention etc. (Armstrong and Moffat, 1983). Irrespective of the mechanisms of tolerance development, clinically it is important to develop nitric oxide donors with least tendency to develop tolerance.

P B Ghosh et al. (Journal of Medicinal Chemistry, 1968) disclosed the method of synthesis of various benzo -2,1,3- oxadiazoles (benzofurazans) and their N-oxides (benzofuroxans) and their potential as antileukemic and immuno-suppressive drugs in vitro.

P B Ghosh et al. (Journal of Medicinal Chemistry, 1972) tested 4- nitro benzofurazans and 4- nitrobenzofuroxans bearing electron withdrawing substitutents in the 5 and 6 position (relative to NO_2) as potential antileukemic and immuno suppressive drugs in vitro.

Nishikawa et al. (The Journal of Pharmacology and Experimental Therapeutics, 1982) disclosed effect of N- ethoxycarbonyl -3- morpholinosydnonimine and its metabolites 3- morpholinosydnonimine, cyanomethyleneamino morpholine, N- nitroso -N- morpholinoamino acetonitrile as novel antianginal agents.

F. Murad (J. Clin. Invest, 1986) disclosed cyclic guanosine monophosphate as a mediator of vasodilation.

James Frampton et al. (Drug Evaluation, Adis International Limited, 1992) gives a review of pharmacology and therapeutic efficiency of nicorandil in angina pectoris. Nicorandil, which has both vasodilator and venodilating properties was found to offer an effective alternative to established vasodilator therapy with conventional nitrates and calcium antagonists in the long term treatment of stable angina pectoris.

US Patent No.5,272,164 disclosed novel carboximidamide derivatives particularly N-cyano-N^1-substituted pyridine carboximidamide derivatives having vasodilating effect and hypotensive effect besides other physiological effects which are helpful in treatment of ischemic heart diseases.

US Patent 5,424,326 disclosed phenyl -1,2,5- oxadiazole carboxamide -2- oxide and its derivatives, which are useful for the treatment of disorders of the cardiovascular system.

F Benedini et. al. (J. Med. Chem. 1995) disclosed a new nitro ester -3- [(nitroxy) alkyl] -2H- 1,3- benzoxazin- 4(3H)- ones showing marked inhibitory activity against ischemia-induced electrocardiographic changes, with only limited systemic hemodynamic effects. These new nitro ester derivatives, endowed with marked anti-anginal activity, which is not associated with concurrent and pronounced fall in systemic blood pressure, are indicative of a new class of selective nitrovasodilators having a preferential action on large coronary vessels, which could be clinically relevant in the treatment of coronary artery diseases.

However, none of the above prior art disclosures on the drugs specifically used as vasodilator for treatment of cardiac ailments tackles the problem associated with the conventional NO-donors to develop tolerance in the patient after continuous use for a period of time. The present invention evaluates the benzofuroxan derivatives for their NO donor activities particularly with reference to their tendency to develop tolerance for continued application of the drug. Significantly, the invention identifies the molecules showing vasodilator activity without tendency to develop tolerance unlike the conventional nitric-oxide donors.

SUMMARY OF THE INVENTION

The present invention provides, in the first aspect, novel benzofuroxan derivatives and pharmaceutically acceptable salts thereof.

Such salts include, but are not limited to, oxalate, tartarate, maleate, methyl sulphonate, p-toluene sulphonate etc.

The invention further provides the use of the benzofuroxan derivatives as tolerance resistant nitric oxide donors.

The invention further provides pharmaceutical formulations comprising benzofuroxan derivatives to be used as tolerance resistant nitric oxide donors.

The invention in a further aspect, provides the process of preparation of the novel benzofuroxan derivatives.

The invention also provides for a method of treatment of mammals including man of coronary heart diseases by administration of a compound of benzofuroxan series.

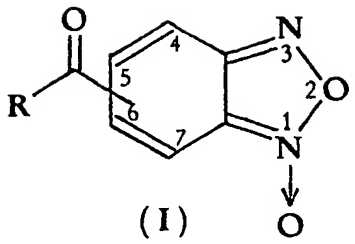
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 gives the dose response curve for the test compound (compound No.1) and GTN.

Fig. 2 gives the dose response curves (percentage relaxation vs the log(M) concentration) for GTN and a test compound No. 1 before and after development of tolerance.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the benzofuroxan series used for cardiovascular disorders are represented by the general formula (I).



(I)

and pharmaceutically acceptable salts thereof

wherein :

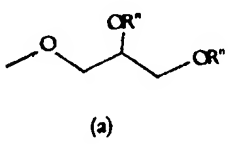
R is -O-$(CH_2)_n$-X-R′;

n = 1 to 6;

X is -NHC(O)-, oxygen or null;

R′ is lower alkyl (C_1-C_8), aromatic, heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two hetero atoms such as nitrogen or oxygen wherein substitution is with lower alkyl,

or R is selected from



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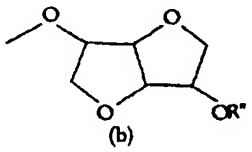

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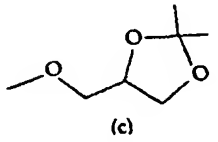

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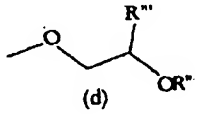

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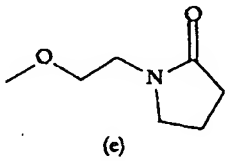
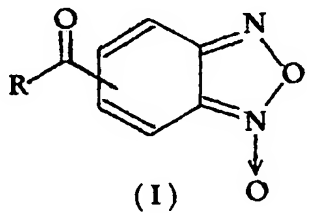


(e)

wherein R'' is hydrogen, nitro, lower alkyl or $-C(O)-R'''$

wherein R''' is hydrogen, lower alkyl or aryl

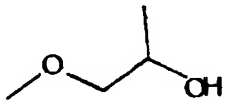
The representative compounds of the invention showing tolerance resistant NO donor activities as defined above are given in the Table-1.



(I)

TABLE - 1

Compound No.	R
1	$-OCH_2CH_2$-NHCO-3-pyridyl.HCl
2	$-OCH_2CH_2$-NHCO-4-pyridyl.HCl
3	substitution (e)
4	substitution (f)
5	$-OCH_2CH_2$-N-morpholinyl.HCl
6	$-OCH_2CH_2OMe$
7	substitution (g)
8	$-OCH_2CH_2O-CH_2CH_3$
9	$-OCH_2$-3-pyridyl.HCl
10	substitution (c)
11	substitution (h)



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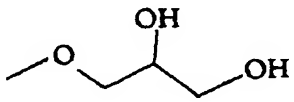

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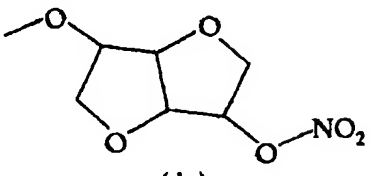


(h)

The present invention also provides a process for the preparation of novel benzofuroxan derivatives of the general formula (I), and their pharmaceutically acceptable salts, wherein one of the processes comprises,

(a) reacting chloro carbonyl benzofuroxan and an alcohol in solvent such as. tetrahydrofuran at room temperature;

(b) adding a base such as triethylamine to the reaction mixture;

(c) refluxing the reaction mixture till the completion of the reaction;

(d) removal of the solvent followed by addition of water and extraction with organic solvent such as ethyl acetate;

(e) concentration of ethyl acetate layer;

(f) purification by column chromatography; and

(g) optionally transforming into the corresponding pharmacologically acceptable salts

Said products of steps (f) and (g) are characterized by m.p. and the conventional spectroscopic techniques.

The present invention also provides a process for the preparation of novel benzofuroxan derivatives of the general formula (I), and their pharmaceutically acceptable salts, wherein the said process comprises,

(a) reacting carboxy benzofuroxan with saturated solution of alcoholic HCl;

(b) removal of excess of alcohol under reduced pressure to get the residue;

(c) purification by column chromatography; and

(d) optionally transforming into the corresponding pharmacologically acceptable salts.

Said products of steps (c) and (d) are characterized by m.p. and the conventional spectroscopic techniques.

Such products can also be prepared by the other equivalent processes of ester formation, which comprises,

(a) reacting carboxy benzofuroxan and an equimolar amount of an alcohol such as N-(2-hydroxyethyl)-nicotinamide, N- (2- hydroxyethyl) isonicotinamide, N-(2-hydroxyethyl) -2-pyrolidinone, N- (2- hydroxyethyl) morpholine, propylene glycol, methylcellosolve, ethylcellosolve, pyridine -3-methanol, solketal, isosorbide -5-mononitrate, etc. in methylene chloride;

(b) adding 4- dimethylamino pyridine and N,N'- dicyclohexyl carbodiimide under stirring and continuing the stirring for a period of 2 to 16 hours at room temperature to complete the reaction;

(c) filtering the reaction mixture when the filtrate on evaporation under reduced pressure gives the crude product;

(d) purifying the product thus obtained by column chromatography; and

(e) optionally transforming into the corresponding pharmaceutically acceptable salts.

The said product of steps (d) and (e) are characterized by m.p. and the conventional spectroscopic techniques.

The invention also provides a process for the preparation of 5(6)- [(2,3- dihydroxy propyloxy) carbonyl] benzofuroxan, (Compound 7), wherein said process comprises,

(a) reacting a mixture of 5(6)- ((±)-2,2- dimethyl -1,3-dioxolane - 4- methyloxy carbonyl) benzofuroxan and acid such as 75% acetic acid and stirring at 80°C for 4 hours;

(b) evaporating the solvent under vacuum to give an oily product; and

(c) purifying the product of step (b) by column chromatography.

Said product of step (c) is characterized by m.p and the conventional spectroscopic techniques.

Pharmaceutical compositions for NO-donor molecules:

The compounds according to this invention as given by general formula (I) or their salts or complexes can be administered orally, intravenously or parenterally as a pharmaceutical preparation in liquid or solid form. It may also be administered via topical, transdermal, sublingual, buccal or rectal route for example as a suppository, ointment, cream, powder, transdermal patch, metered aerosol or spray.

The pharmaceutically acceptable carriers present in the composition of this invention are materials recommended for the purpose of administering the medicament. These may be liquid or solid materials, which are otherwise inert or medically acceptable and are compatible with the active ingredients.

EVALUATION OF THE BIOLOGICAL ACTIVITY:

Methods:

a) In vitro Screening of NO Donors

The method adopted was a modified method of Nishikawa et al (1982). Albino rabbits of either sex were stunned and exsanguinated. Thoracic aorta was quickly removed and cut helically (at an angle of 45°) into strips 4-5 mm wide and 25 to 30 mm long, after removal of adventitial connective tissue. The endothelium was rubbed off gently using a cotton swab soaked in Kreb's solution. Two strips were fixed vertically in organ baths containing 20 ml. Kreb's solution maintained at 37°C and bubbled with oxygen. A resting tension of 4 g was applied and the preparation was allowed to equilibrate for 30min. Each preparation was exposed to two primer doses

of KCl (30mM). After the contraction reached a maximum, the bath was drained off and replaced with fresh Kreb's solution. Half an hour later, cumulative dose response curve for the test compound was taken on one tissue (test) and for glyceryl trinitrate (GTN) in the other (standard). The dose range used was from 10^{-9} M to 10^{-3} M with a contact period of 4 min. for each dose. After the maximum relaxation was achieved with the last dose, papaverine (10^{-4} M) was added to obtain the maximum relaxation.

Tolerance was induced in both the tissues by adding 440 µM of GTN for 90 minutes. During this period the bath solution was changed every 30 min. and 440 µM of GTN was replaced. Later both the tissues were washed thoroughly and the dose response curve (DRC) for both the test and the standard were repeated. The percentage relaxation with individual doses was calculated by taking the maximum relaxations to 10^{-4} M papaverine as 100% relaxation. A graph was plotted by taking the percentage relaxation vs the log (M) concentration of the compounds. The relaxant activity of the test compound was assessed by calculating the mean relative potencies (MRP) and the mean activity ratio (MAR), both before and after tolerance, as defined below:

$$\text{MRP} = \frac{\text{Concentration of GTN producing 50\% of its maximum relaxation}}{\text{Concentration of test compound producing 50\% of the maximum relaxation of GTN.}}$$

$$\text{MAR} = \frac{\text{Maximum relaxation produced by the test compound}}{\text{Maximum relaxation produced by GTN}}$$

Selection criteria for in vivo study: Compounds having MRP greater than 3 and MAR greater than 1.3 after tolerance were selected for in vivo study. Dose response curve for compound 1 is given in Figs. 1 and 2 of the accompanying drawings as an example for the estimation of MRP and MAR.

b) In vivo Pharmacological Screening:

A modified method of Benedini et al (1995) was adopted for studying the anti-anginal effect of the chosen compounds. Guinea pigs of either sex, weighing approximately 400-600 g were used for this study. Animals were anesthetized with urethane (1.25 g/kg, i.p.) and jugular vein was cannulated for intravenous administration of drugs/vehicle. Mean arterial blood pressure (MABP) was monitored by a cannula inserted into the right carotid artery and connected to a pressure transducer. Standard limb lead II electrocardiogram was recorded continuously. All the recordings were carried out on a MacLab system (AD Instruments, UK).

The ability of the test compounds to suppress the vasopressin induced T-wave elevation was used as the model for studying the anti-anginal effects of the compounds. Guinea pigs were divided into two groups for the purpose of this study, i) control group (pretreated with the vehicle for the compound) and ii) drug treated group.

i) Control Group

In this group of animals the solvent used for dissolving the test compound was administered intravenously in a volume of 1 ml/kg. The basal T-wave heights, heart rates and MABP and changes after vehicle administration were noted. Thirty seconds later 1 I.U./ ml/kg of vasopressin was administered intravenously. The T-wave

heights, heart rates and MABP and their changes after vasopressin administration were also noted. The T-wave elevation (after vasopressin administration), maximum rise in MABP, and changes in heart rate were calculated from the above data and expressed as mean ± standard deviation.

ii) Drug treated group

The effects of the test compound in suppressing the T-wave elevation caused by vasopressin were evaluated with atleast three dose levels. Groups of 6 guinea pigs were used for each dose. The test compound was injected 30 seconds prior to vasopressin administration. Changes in MABP, heart rate and T-waves were recorded as described for the control group. The percentage inhibition of vasopressin induced T-wave elevation was calculated for each dose taking the T-wave height estimated in control group as 100%. From the dose vs percent inhibition relationship, the dose required for 50% inhibition (ED_{50}) for the T-wave elevation was estimated.

Determination of the ED_{20} values for drop in MABP

In a separate group of animals the drop in MABP after administration of the test compound (dose range of 0.1 - 1000 µg/kg, i.v.) was studied. Atleast three animals were used for each dose. Care was taken so that the doses were given only after the MABP had stabilized from the effects of the previous dose. All doses were injected in a final volume of 1 ml/kg. The drop in MABP was noted for increasing concentrations of the test compound and a dose response curve was drawn. From this graph the dose required to produce a 20% fall in MABP (ED_{20}) was calculated.

The specificity of the test compound was defined by the selectivity index, which was calculated as shown below:

$$\text{Selectivity Index} = \frac{\text{Dose required for 20\% reduction in MABP (µg/kg)}}{\text{Dose required for 50\% inhibition of T-wave elevation (µg/kg.)}}$$

Compounds having selectivity ratio greater than 30 times that of GTN were selected for initial toxicology evaluation. The selectivity index for GTN was estimated to be 0.017.

Results of in vitro Screening of NO Donors:

The results of in vitro screening of the NO donors are given in the following Table 2.

TABLE 2 - In vitro activity of NO donors

Compound No.	Mean Relative Potency		Mean Activity Ratio	
	Before Tolerance	After Tolerance	Before Tolerance	After Tolerance
1	0.2	8.4	1.3	1.7
2	0.06	6.94	1.19	2.38
3	0.11	25	1.15	1.83
4	0.28	11.22	1.13	1.69
5	0.18	4.17	1.08	1.22
6	0.97	17.02	1.74	2.32
7	0.17	3.49	1.16	1.58
8	0.2	11.9	1.04	1.97
9	0.53	8.05	1.23	1.7
10	0.39	10.13	1.05	1.57
11	0.25	7	1.37	1.63

Results of in vivo evaluation:

The compounds, which were selected based on in-vitro studies, were subjected to in-vivo studies to assess their anti-anginal action. Compounds with sufficient selectivity (i.e. lower hypotension) and anti-anginal action are listed in Table - 3.

TABLE 3 - In vivo activity of selected Nitric Oxide donors

Compound	Dose needed for 20% fall in B.P. (ED_{20} µg/kg, i.v.) (A)	Dose required for 50% inhibition of T-wave (ED_{50} µg/kg, i.v.) (B)	Selectivity Index A/B (C)
GTN	8.22	474.40	0.017
1	458.02	886.42	0.517
3	139.52	675.61	0.152
6	226.34	337.90	0.67
9	227.16	372.85	0.61
10	286.00	492.00	0.58

It was observed that compounds 1, 6, 9 and 10 have a high selectivity index as compared to GTN. In the case of these compounds, the index is significantly higher. The index showed that these compounds could elicit anti-anginal activity at a dose, which had minimum systemic effects. Their selectivity in dilating the coronary arteries was quite high as compared to a conventional drug like GTN.

The high selectivity index of these compounds as compared to nitroglycerine show that they selectively dilate the coronary arteries and have a lower tendency to cause hypotension during clinical usage. For example, compound 1 is 30 times more selective as compared to GTN. This shows that these compounds have very little tendency to cause hypotension. Conventional nitrates like GTN cause tachycardia, retrosternal discomfort, palpitations, collapse, syncope and postural hypotension, etc as a manifestation of hypotensive effect. This could limit their use in selected patients. However, the compounds described in this invention due to a lower tendency to cause hypotension are superior to conventional nitrates.

The benzofuroxans described in this invention can be used in cardiovascular disorders like acute effort angina, angina prophylaxis, mixed angina and silent ischemia, acute myocardial infarction, congestive heart failure, etc. They can be used alone or in combination with beta adrenergic blockers like propranolol, atenolol, carvedilol, etc. and calcium channel antagonists like verapamil, diltiazem, etc.

The following examples are presented to further illustrate the invention but do not limit it in any way.

The method of preparation of the novel compounds of this invention are given in the following examples:

EXAMPLE 1: Preparation of 5(6)-(2-nicotinamide ethyloxycarbonyl) benzofuroxan hydrochloride (Compound 1):

In 20 ml of methylene chloride, 0.9 g of 5(6)- carboxy benzofuroxan was added at room temperature. To this solution was added 0.83 g of N-2- hydroxyethyl nicotinamide. Then 1.1 g of dicyclohexyl carbodiimide and 4-dimethylaminopyridine (70 mg) were added at room temperature and the reaction mixture was stirred at room temperature for 16 hours. Methylene chloride was removed on a rotary evaporator under reduced pressure to give a gummy material which was purified by column chromatography using hexane:ethyl acetate (5:7) to give 300 mg of solid.

100 mg of the above solid was dissolved in 10 ml of methanol at 0°C. To it was added 5 ml of methanolic HCl solution and the reaction mixture was warmed to room temperature and stirred for 15 minutes to give 90 mg of 5(6)- (2-nicotinamide ethyloxycarbonyl) benzofuroxan hydrochloride.

m. p. : 202 - 205°C.

IR(KBr) : 1711, 1666, 1607, 1576, 1547, 1020 cm^{-1}

PMR ($CDCl_3$, 300 MHz) δ: 8.99 (1H,s), 8.75 (1H,s), 8.23 (1H,s), 8.13 (1H,d,J=9Hz), 7.85 (1H,s), 7.4 (2H,s), 6.85 (1H,s), 4.6 (2H,s), 3.92 (2H,s)

Alternatively, compound 1 can also be prepared by following procedure.

5(6)-Chlorocarbonyl benzofuroxan (100 mg) and N-2-hydroxy ethyl nicotinamide (150 mg) were dissolved in THF (10 ml) at room temperature. To the reaction mixture triethylamine (0.1 ml) was added and reaction mixture was refluxed for 24 hrs. THF was removed under reduced pressure. To the residue 10 ml water was added and extracted with ethyl acetate (3 x 20 ml). Ethyl acetate was removed under reduced pressure to get sticky mass which was purified by column chromatography using EtOAc: n-hexane (90:10) to give 65 mg of compound 1.

EXAMPLE 2: Preparation of 5(6)- (2- isonicotinamideethyloxycarbonyl) benzofuroxan. (Compound 2):

5(6)- Carboxy benzofuroxan (1.8g, 0.01 mole) and N- (2-hydroxyethyl) isonicotinamide (1.66 g, 0.01 mole) were dissolved in CH_2Cl_2 (100 ml) and THF (100 ml) mixture. To this solution, 4-dimethylamino pyridine (70 mg) and N,N'-dicyclohexyl carbodiimide (3 g, 0.0145 mole) were added under stirring. The reaction mixture was stirred for 16 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product which was purified by column chromatography (EtOAc:n- hexane = 90:10) to give the title compound as yellow solid (0.2 g, 74%).

m.p.: 201°C (HCl salt)

IR (KBr): 3423, 3180, 1720, 1677, 1613, 1585, 1543, 1490 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 2.58-2.6 (2H,t,J=1.7Hz), 3.55 (1H,s), 4.52-4.57 (2H,t,J=5.26Hz), 7.67-8.45 (3H,m), 8.95-9.65 (4H,dd)

Mass: 328 (M^+), 298, 229, 181, 164, 147, 117, 105, 77, 50.

EXAMPLE 3: Preparation of 5(6)- (2- pyrolidinone ethyloxy carbonyl) benzofuroxan. (Compound 3):

5(6)- Carboxy benzofuroxan (0.9g, 0.005 mole) and 1- (2- hydroxyethyl) -2-pyrolidinone (0.7 g, 0.005 mole) were dissolved in CH_2Cl_2 (40 ml). To this solution, 4- dimethyl amino pyridine (70 mg) and N,N'- dicyclohexyl carbodiimide (2.06 g, 0.01 mole) were added under stirring. The reaction mixture was stirred for 3 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product, which was purified by column chromatography (EtOAc:n- hexane = 50:50) to give the title compound as pale yellow solid (0.7 g, 48%).

m.p.: 101-102°C

IR (KBr): 1726, 1678, 1611, 1590, 1534 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 1.99-2.14 (2H,m), 2.35-2.43 (2H,t,J=7.72Hz), 3.49-3.56 (2H,t,J=6.9Hz), 3.68-3.73 (2H,t,J=5.2Hz), 4.48-4.53 (2H,t,J=5.4Hz), 7.6-7.86 (3H,m)

Mass: 291 (M^+), 273, 225, 111, 98, 70, 56.

EXAMPLE 4: Preparation of 5(6)- (2- hydroxy propyloxy carbonyl) benzofuroxan. (Compound 4):

5(6)- Carboxy benzofuroxan (1.8 g, 0.01 mole) and propylene glycol (0.76 g, 0.01 mole) were dissolved in CH_2Cl_2 (80 ml). To this solution, 4- dimethylamino pyridine (140 mg) and N,N'- dicyclohexyl carbodiimide (4.4 g, 0.021 mole) were added with stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product

which was purified by column chromatography (EtOAc:n- hexane = 20:80) to give the title product as pale yellow solid (1.16 g, 49%)

m.p.: 89-90°C

IR (KBr): 3500-3100, 1716, 1654, 1613, 1592, 1540, 1491 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 1.3-1.33 (3H,d,J=6Hz), 3.82 (1H,s), 4.22-4.4 (3H,m), 7.6-8.26 (3H,m)

Mass: 238 (M^+), 179, 163, 147, 103, 75, 58, 45.

EXAMPLE 5: Preparation of 5(6)- (2- morpholino ethyloxy carbonyl) benzofuroxan. (Compound 5):

5(6)- Carboxy benzofuroxan (0.9 g, 0.005 mole) and N-(2- hydroxyethyl) morpholine (0.71 g, 0.005 mole) were dissolved in CH_2Cl_2 (50 ml). To this solution, 4-dimethylamino pyridine (70 mg) and N, N'- dicyclohexyl carbodiimide (2.06 g, 0.01 mole) were added under stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product which was purified by column chromatography (EtOAc:n- hexane = 50:50) to give the title compound 5 as white solid (0.5 g, 34%)

The base (0.2 g) was transformed into the corresponding HCl salt, by 5% methanolic HCl (0.14 g, 64%)

m.p.: 210°C (HCl salt)

IR (KBr): 1729, 1613, 1589, 1542 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 2.58-2.59 (4H,t,J=4.5Hz), 3.18-3.2 (4H,t,J=13.63Hz), 3.55-3.43 (2H,t), 3.97-4.17 (2H,t), 7.48-7.98 (3H,m)

Mass: 293 (M^+), 113, 103, 101, 100.

EXAMPLE 6: Preparation of 5(6)- (2-methyloxy ethyloxy carbonyl) benzofuroxan. (Compound 6):

5(6)- Carboxy benzofuroxan (1.8 g, 0.01 mole) and methyl cellosolve (0.076 g, 0.01 mole) were dissolved in CH_2Cl_2 (60 ml). To this solution, 4- dimethylamino pyridine (0.3 g) and N,N'-dicyclohexyl carbodiimide (2.3 g, 0.01 mole) were added with stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product as oily liquid. Crude product was purified by column chromatography (EtOAc:n-hexane = 5:95) to give the title compound. It was crystallized from n- hexane to yield 5(6)-methyloxy ethyloxy carbonyl benzofuroxan as yellow solid (1.2 g, 50%).

m.p.: 68-69°C

IR (KBr): 1717, 1615, 1582, 1536 cm^{-1}

PMR (300 MHz, $CDCl_3$) δ: 3.43 (3H,s), 3.72-3.75 (2H,t,J=6Hz), 4.5- 4.53 (2H,t,J=6Hz), 7.26-8.26 (3H,m).

Mass: 238 (M^+), 207, 180, 163, 103, 75, 58.

Alternatively, compound 6 can also be prepared by following procedure:

5(6)-Carboxy benzofuroxan (1.0 g) was heated to 80° C in a saturated solution of methyl cellosolve HCl for 16 hours. Excess methyl cellosolve was removed under vacuum and the residue was redissolved in diethylether and washed with aqueous NaOH, followed by water and dried over Na_2SO_4. Ether was removed under vacuum and the residue was purified by column chromatography to get 280 mg. of compound 6.

EXAMPLE 7: Preparation of 5(6)- (2,3- dihydroxy propyloxy carbonyl) benzofuroxan. (Compound 7):

A mixture of 5(6)-((±)-2,2- dimethyl -1,3- dioxolane -4-methyloxy carbonyl) benzofuroxan (0.5 g, 0.001 mole) and 5 ml of 75% acetic acid was stirred at 80°C for 4 hours. Evaporation of the solvent under vacuum (40°C) gave oily product, which was purified by column chromatography (hexane:EtOAc = 80:20) to give the title compound as yellow solid (0.4 g, 93%)

m.p.:86°C

IR (KBr): 3355, 1719, 1606, 1450 cm^{-1}

PMR (300 MHz, $CDCl_3$) δ: 3.89-3.90 (1H,d,J=4.2Hz), 4.03-4.06 (1H,t,J=4.5Hz), 4.36-4.52 (2H,m), 7.61-8.34 (3H,m)

Mass: 254 (M^+), 180, 163, 103

EXAMPLE 8: Preparation of 5(6)- (2- ethoxy ethyloxy carbonyl) benzofuroxan. (Compound 8):

5(6)- Carboxy benzofuroxan (1.8 g, 0.01 mole) and ethylcellosolve (0.8 g, 0.01 mole) were dissolved in CH_2Cl_2 (50 ml). To this solution, 4- dimethylamino pyridine (0.3g) and N,N'- dicyclohexyl carbodiimide (2.4 g, 0.011 mole) were added under stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product as brown oily liquid, which was purified by column chromatography (EtOAc:n- hexane = 20:80) to yield the title compound as pale yellow viscous oil (1.0 g, 40%)

IR (KBr): 1727, 1598, 1538, 1488cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 1.2-1.27 (3H,t,J=7Hz), 3.54-3.64 (2H,q,J=7Hz), 3.76-3.81 (2H,t,J=6Hz), 4.5-4.54 (2H,t,J=5Hz), 7.59-8.26 (3H,m)

EXAMPLE 9: Preparation of 5(6)- (3- pyridine methoxy carbonyl) benzofuroxan. (Compound 9):

5(6)- Carboxy benzofuroxan (1.8 g, 0.01 mole) and pyridine -3- methanol (1.1 g, 0.01 mole) were dissolved in CH_2Cl_2 (50 ml). To this solution, 4- dimethylamino pyridine (70 mg) and N,N'-dicyclohexyl carbodiimide (3 g, 0.014 mole) were added with stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product, which was purified by column chromatography (EtOAc:n- hexane = 25:75) to give the title compound as a pale yellow solid. The base (0.5 g) was transformed into the corresponding HCl salt, by 5% methanolic HCl (0.4 g, 71%)

m.p.: 200°C (HCl salt)

IR (KBr): 1719, 1616, 1589, 1534 cm^{-1}

PMR (300 MHz, $DMSOd_6$) δ: 5.59 (2H,s), 7.88-8.04 (3H,m), 8.63-9.09 (4H,m)

Mass: 307 (M^++HCl), 271 (M^+), 180, 92.

EXAMPLE 10: Preparation of 5(6)-((±)-2,2- dimethyl -1,3-dioxolane-4- methyloxy carbonyl) benzofuroxan. (Compound 10):

5(6)- Carboxy benzofuroxan (0.99 g, 0.005 mole) and solketal (0.66 g, 0.005 mole) were dissolved in CH_2Cl_2 (40 ml). To this solution, 4- dimethylamino pyridine (0.2 g) and N,N'- dicyclohexyl carbodiimide (1.33 g, 0.006 mole) were added under stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product as oily liquid, which was purified by column chromatography (EtOAc:n- hexane = 10:90) to give the title compound as pale yellow solid (0.6 g, 41%)

m.p.: 51-52°C

IR (KBr): 1725, 1586, 1535, 1484 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 1.39 (3H,s), 1.46 (3H,s), 3.83-3.89 (1H,dd,6Hz), 4.13-4.20 (1H,dd,6Hz), 4.39-4.48 (3H,m), 7.85-8.27 (3H,m)

Mass: 294 (M^+), 279, 163.

EXAMPLE 11: Preparation of 5(6)-(isosorbide mononitrateoxy carbonyl) benzofuroxan. (Compound 11):

To a solution of 5(6)- carboxy benzofuroxan (1.0 g, 0.0055 mole) and isosorbide - 5- mononitrate (0.09 g, 0.0047 mole) in CH_2Cl_2 (50 ml) were added 4- dimethylamino pyridine (50 mg) and N,N'- dicyclohexyl carbodiimide (2 g, 0.0097 mole) with stirring. The reaction mixture was stirred for 2 hours at room temperature. It was filtered and the filtrate on evaporation under reduced pressure gave crude product, which was purified by column chromatography (EtOAc:n-hexane = 20:80) to give the title product as a yellow solid (1.0 g, 51%)

m.p.: 117-118°C

IR (KBr): 1721, 1635, 1590, 1537 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: 3.91-4.16 (4H,m), 4.63-4.66 (1H,d,J=6Hz), 5.07-5.12 (1H,dd,J=4.5Hz), 5.39-5.68 (2H,m), 7.61-8.36 (3H,m)

Mass: 353 (M^+), 194, 163, 127.

Oral Formulations:

Orally they may be administered as solid dosage forms for example as pellets, granules, powder, sachet or as discreet units such as tablets or capsules, etc.. Other orally administered pharmaceutical preparations include monophasic and biphasic liquid dosage forms either in ready to use form, or forms suitable for reconstitution such as mixtures, syrups, suspensions or emulsions. The preparations in addition may contain diluents, dispersing agents, buffers, stabilizers, solubilizers, surface active

agents, preservatives, chelating agents and/or other pharmaceutical additives. Aqueous or non aqueous vehicles or their combination may be used and if desired may contain suitable sweeteners, flavouring agents or similar substances. In the case of a suspension or emulsion a suitable thickening agent, suspending agent or emulsifying agent may be present. Pharmaceutical preparations can have a slow, delayed or controlled release of active ingredients as is provided by a matrix or diffusion controlled system.

Parenteral formulations:

For parenteral administration, the compounds or their salts or suitable complexes may be presented in a sterile vehicle which may be an aqueous or non aqueous vehicle or a combination thereof. The examples of vehicles are, water, ethyl oleate, oils and derivatives of polyols, glycols and their derivatives. It may contain additives common in injectable preparations like stabilizers, solubilizers, pH modifiers, buffers, antioxidants, cosolvents, complexing agents, tonicity modifiers, etc. Some suitable additives are, for example tartrate, citrate, or similar buffers, alcohols, sodium chloride, dextrose and high molecular weight liquid polymers. Another alternative is sterile powder for reconstitution. The compound may be administered in the form of injection, intravenous infusion/drip, or suitable depot preparation.

When the present invention, its salts or a suitable complex is presented as a discrete unit dosage form like a tablet, it may contain in addition medically inert excipients as are used in art. Diluents such as starch, lactose dicalcium phosphate, lubricants or similar additives like talc, magnesium stearate, polymeric substances like methyl cellulose, hydroxy propyl cellulose, fatty acids and derivatives, sodium starch glycollate, etc. can also be used.

EXAMPLE 12: Preparation of oral dosage form of the benzofuroxan derivatives given in Table 1.

The compounds described in Table 1 can be prepared in the form of tablets, containing the active ingredient in the range of 0.03 to 3 mg per tablet. A typical tablet has the following composition:

Active ingredient	as given above
Starch	27 mg
Lactose	70 mg
Polyvinyl pyrolidone (k-30)	1.0 mg
Talc	1.5 mg
Magnesium stearate	0.5 mg

EXAMPLE 13: Preparation of parenteral dosage form of benzofuroxan derivatives given in Table 1:

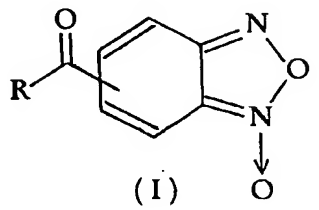
A preparation suitable for parenteral administration has the following composition:

Active ingredient	1 mg.
Poly ethylene glycol - 400	0.5 ml
Isotonic saline solution q.s.	
or water for injection	1 ml

These examples are presented by way of illustration alone and in no way limit the scope of the invention.

I CLAIM:

1. A novel compound of the benzofuroxan series used for cardiovascular disorders represented by the general formula (I)



(I)

and pharmaceutically acceptable salts thereof

wherein:

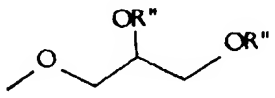
R is -O-(CH_2)n-X-R';

n = 1 to 6;

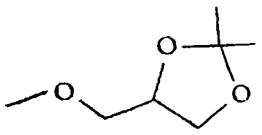
X is -NHC(O)-, oxygen or null;

R' is lower alkyl (C_1-C_8), aromatic, heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two hetero atoms such as nitrogen or oxygen wherein substitution is with lower alkyl ;

or R is selected from



(a)



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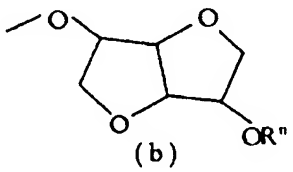

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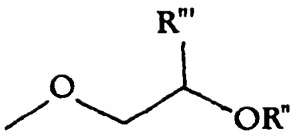

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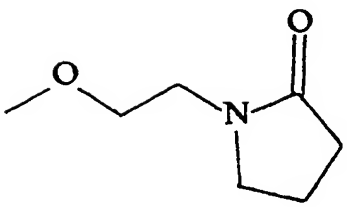


(e)

wherein R'' is hydrogen, nitro, lower alkyl or -C(O)-R'''

wherein R''' is hydrogen, lower alkyl or aryl

2. A compound as claimed in claim 1, wherein the preferred position for the substitution is 5(6).

3. A compound as claimed in claim 1 or 2, wherein

X is -NHC(O)-;

R' is lower alkyl (C_1-C_8), heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two hetero atoms such as nitrogen or oxygen wherein substitution is with lower alkyl and the preferred value of n is 1 and 2.

4. A compound as claimed in claim 1, 2, or 3, wherein said compound is 5(6)-(2-nicotinamide ethyloxycarbonyl) benzofuroxan hydrochloride.

5. A compound as claimed in claim 1 or 2 wherein said compound is 5(6)-(3-pyridine methoxy carbonyl) benzofuroxan.

6. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-((±)-2,2-dimethyl-1, 3-dioxalane-4-methyloxycarbonyl) benzofuroxan.

7. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-pyrolidinone ethyloxy carbonyl) benzofuroxan.

8. A compound as claimed in claim 1, 2 or 3,wherein said compound is 5(6)-(2-isonicotinamide ethyloxy carbonyl) benzofuroxan hydrochloride.

9. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-ethoxy ethyloxy carbonyl) benzofuroxan.

10. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-hydroxy propyloxy carbonyl) benzofuroxan.

11. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(isosorbide mononitrateoxycarbonyl) benzofuroxan.

12. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2,3-dihydroxy propyloxy carbonyl) benzofuroxan.

13. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-methyloxy ethyloxy carbonyl) benzofuroxan.

14. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-morpholino ethyloxy carbonyl) benzofuroxan.

15. A process for the preparation of the benzofuroxan derivatives of general formula (I) as defined in claim 1 which comprises:

reaction of carboxy benzofuroxan and the corresponding alcohol in the presence of 4-dimethylamino pyridine and N,N'-dicyclohexylcarbodiimide.

16. A process for the preparation of the benzofuroxan derivatives of general formula (I), as defined in claim 1 which comprises :

reaction of chloro carbonyl benzofuroxan and the corresponding alcohol in the presence of a base such as trimethylamine and an organic solvent.

17. A process for the preparation of the selected benzofuroxan derivatives of general formula (I) as defined in claim 1, which comprises:

reaction of the carboxybenzofuroxan in the solution of corresponding alcoholic HCl.

18. A process for the preparation of 5(6)-[(2,3-dihydroxy propyloxy)carbonyl] benzofuroxan of general formula (I) as defined in claim 1, which comprises:

cleavage of the ketal, 5(6)-((±)-2,2-dimethyl-1,3-dioxolane-4-methyloxy carbonyl) benzofuroxan under mild acidic condition at appropriate temperature in a suitable solvent.

19. The process as claimed in claims 15, 16, 17 or 18, wherein the compound so obtained can be converted into a pharmaceutically acceptable salt thereof.

20. The use of compound of general formula (I)as claimed in claim 1, in cardiovascular disorders like coronary heart diseases.

21. The use of compound of general formula (I)as claimed in claim 20, as a tolerance resistant anti-anginal compound.

22. The use as claimed in claim 20 or 21 wherein said compound is 5(6)- (2-nicotinamide ethyloxycarbonyl) benzofuroxan hydrochloride.

23. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(3-pyridine methoxy carbonyl)-benzofuroxan.

24. The use as claimed in claim 20 or 21 wherein said compound is 5(6)-((±)-2,2-dimethyl-1, 3-dioxalane-4-methyloxycarbonyl) benzofuroxan.

25. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2-pyrolidinone ethyloxy carbonyl)benzofuroxan.

26. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2-isonicotinamide ethyloxy carbonyl)benzofuroxan hydrochloride.

27. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2-ethoxy ethyloxy carbonyl)benzofuroxan.

28. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2-hydroxy

propyloxy carbonyl)benzofuroxan.

29. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(isosorbide mononitrateoxycarbonyl)benzofuroxan.

30. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2,3-dihydroxy propyloxy carbonyl)benzofuroxan.

31. The use as claimed in claim 20 or 21, wherein said compound is 5(6)-(2-methyloxy ethyloxy carbonyl)benzofuroxan.

32. A pharmaceutical composition of the compounds of general formula (I) as claimed in claim 1, wherein the said composition contains pharmaceutically active amount of the compound of general formula (I) and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition as claimed in claim 32 in the form of an oral formulation.

34. The pharmaceutical composition as claimed in claim 33, wherein said pharmaceutically acceptable carrier is selected from one or more of the compounds like starch, lactose, polyvinyl pyrolidone (k-30), tale and magnesium stearate.

35. The pharmaceutical composition as claimed in claim 32 in the form of a parenteral formulation.

36. The process for the preparation of a parenteral formulation, as claimed in claim 35, which comprises dissolution of the active ingredient of general formula (I) in polyethylene glycol 400 and diluting the solution so obtained, with an isotonic solution or water to the desired concentration.

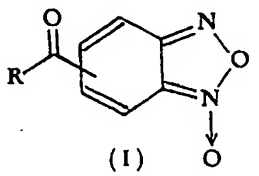
37. A method for the treatment of mammal, including man, of coronary heart diseases comprising administration of an effective amount of a compound I as defined in claim 1.

AMENDED CLAIMS

[received by the International Bureau on 02 November 1999 (02.11.99) ;
original claim 1 amended ; remaining claims unchanged (2 pages)]

I CLAIM:

1. A novel compound of the benzofuroxan series used for cardiovascular disorders represented by the general formula (I)



(I)

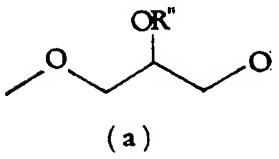
and pharmaceutically acceptable salts thereof
wherein:
R is -O-(CH_2)n-X-R';

n = 1 to 6;

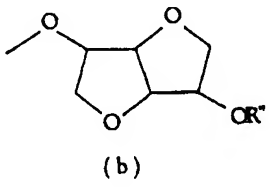
X is -NHC(O)- or oxygen;

R' is lower alkyl (C_1-C_8), aromatic, heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two hetero atoms such as nitrogen or oxygen wherein substitution is with lower alkyl ;

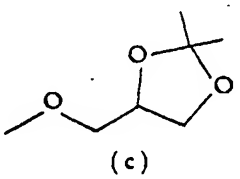
or R is selected from



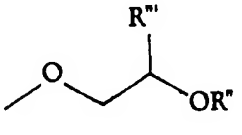
(a)



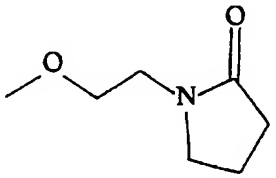
(b)



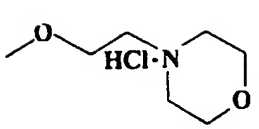
(c)



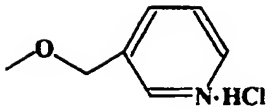
(d)



(e)



(f)



(g)

wherein R" is hydrogen, nitro, lower alkyl or -C(O)-R'''

wherein R''' is hydrogen, lower alkyl or aryl

2. A compound as claimed in claim 1, wherein the preferred position for the substitution is 5(6).

3. A compound as claimed in claim 1 or 2, wherein

X is -NHC(O)-;

R' is lower alkyl (C_1-C_8), heteroaromatic, substituted or unsubstituted saturated heterocyclic ring with one or two hetero atoms such as nitrogen or oxygen wherein substitution is with lower alkyl and the preferred value of n is 1 and 2.

4. A compound as claimed in claim 1, 2, or 3, wherein said compound is 5(6)-(2-nicotinamide ethyloxycarbonyl) benzofuroxan hydrochloride.

5. A compound as claimed in claim 1 or 2 wherein said compound is 5(6)-(3-pyridine methoxy carbonyl) benzofuroxan.

6. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-((±)-2,2-dimethyl-1, 3-dioxalane-4-methyloxycarbonyl) benzofuroxan.

7. A compound as claimed in claim 1 or 2, wherein said compound is 5(6)-(2-pyrolidinone ethyloxy carbonyl) benzofuroxan.

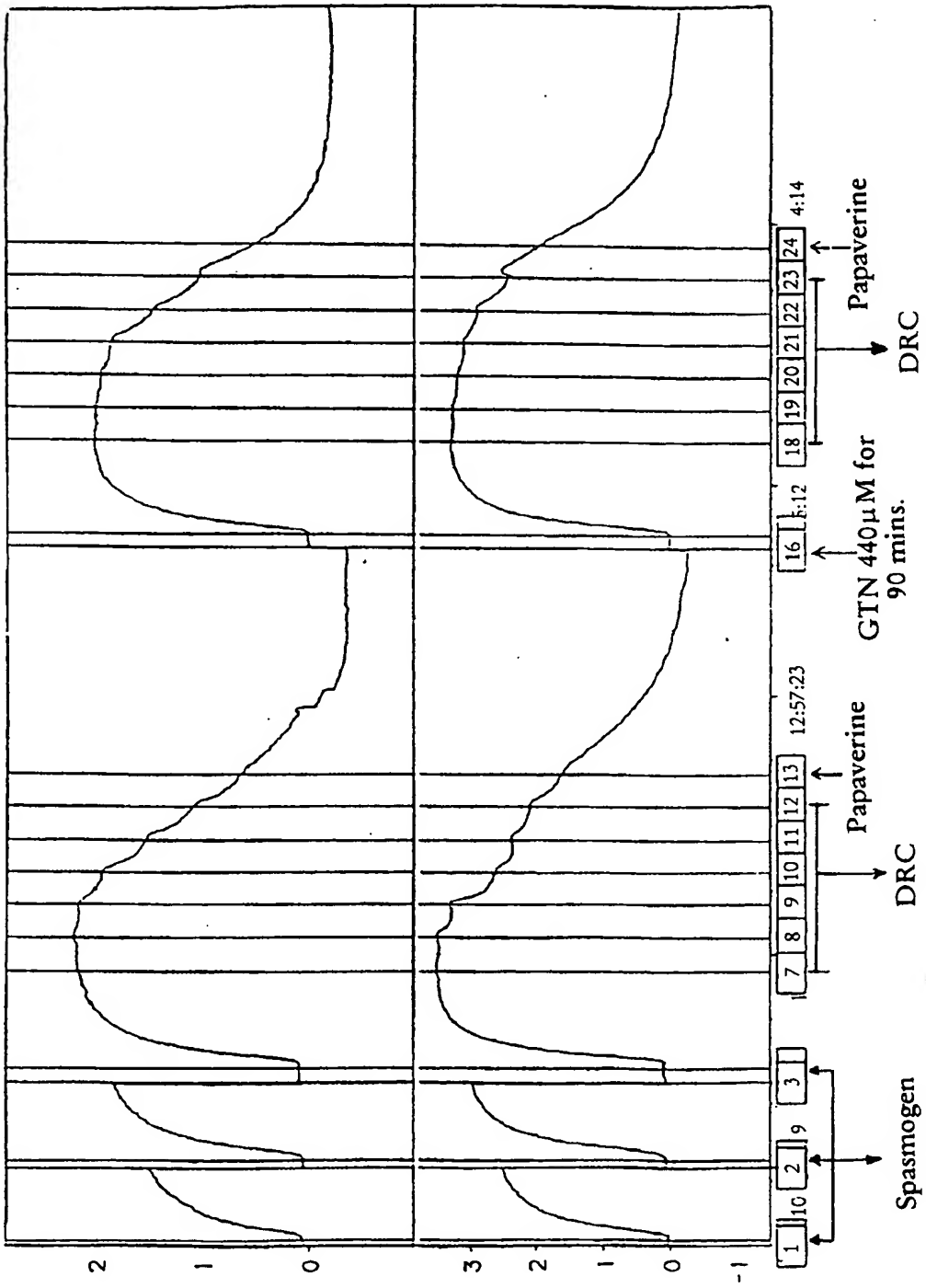
8. A compound as claimed in claim 1, 2 or 3,wherein said compound is 5(6)-(2-isonicotinamide ethyloxy carbonyl) benzofuroxan hydrochloride.

STATEMENT UNDER ARTICLE 19

Claim 1 has been amended to define the scope of the invention more clearly and precisely. This is done by deletion of "null" option from the definition of X in the substituent R = $-O-(CH_2)_n-X-R^1$ in the compound of general formula I, and with addition of two specific structural moieties represented by (f) and (g) in the definition of R to define the specific compounds Nos.5 and 9 of the invention respectively.

Such amendments will necessitate corresponding amendments in the statement of invention appearing on pages 5-7 of the specification and also Table 1 on page 7 to indicate that the substituent R for compounds Nos.5 and 9 may be structurally represented by (f) and (g). Consequently, the structures (f), (g) and (h) now appearing on page 7 are required to be relabelled as (h), (i) and (j) respectively to maintain the alphabetical order and to uniquely represent each structural moiety with necessary amendments in Table 1 to represent compounds Nos.4, 7 and 11.

1/2



Compound No 1 GTN Fig - 1

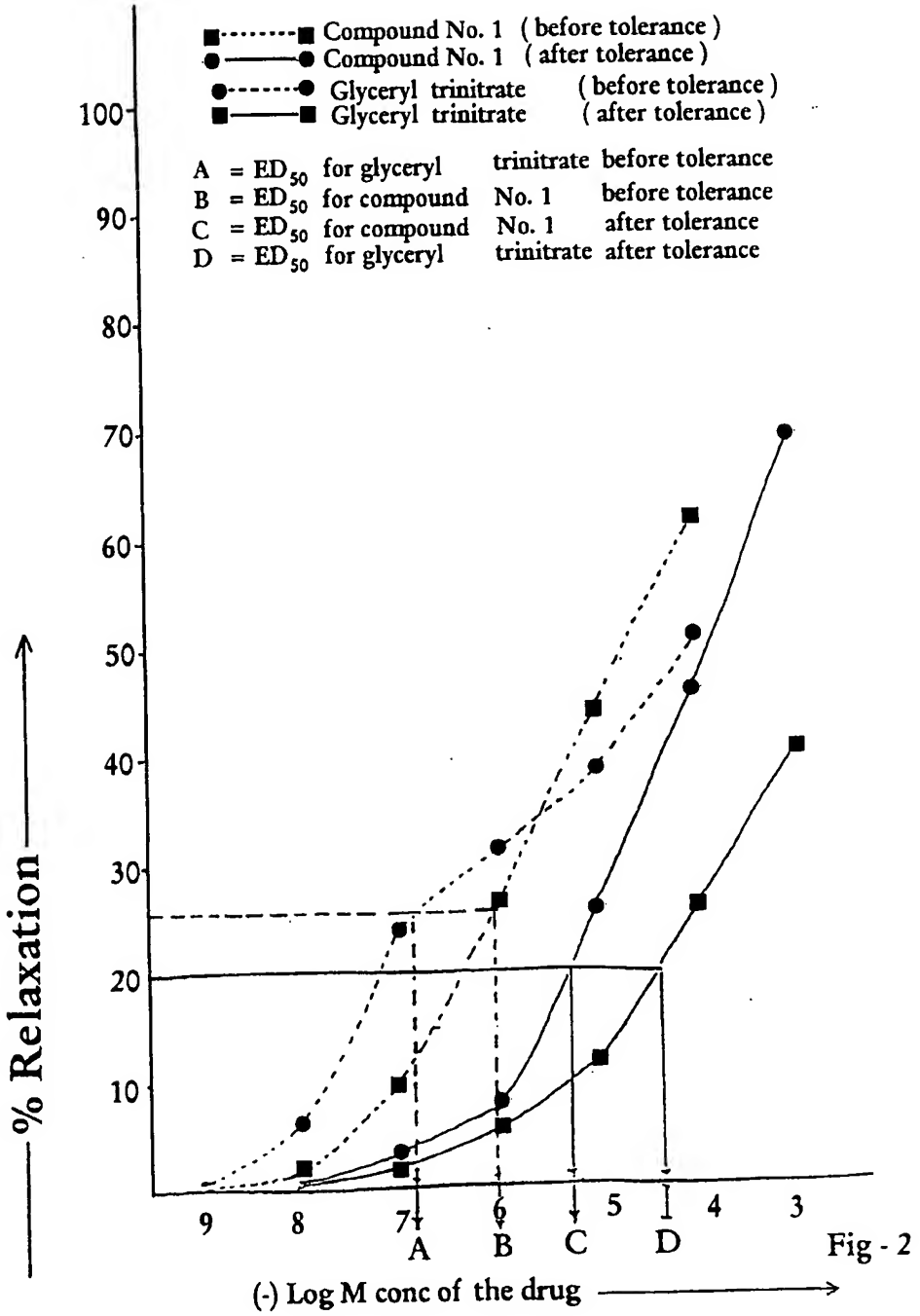

Compound No. 1 (before tolerance)
Compound No. 1 (after tolerance)
Glyceryl trinitrate (before tolerance)
Glyceryl trinitrate (after tolerance)
A = ED50 for glyceryl trinitrate before tolerance
B = ED50 for compound No. 1 before tolerance
C = ED50 for compound No. 1 after tolerance
D = ED50 for glyceryl trinitrate after tolerance
% Relaxation
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
A
B
C
D
(-) Log M conc of the drug

Fig - 2

INTERNATIONAL SEARCH REPORT

Inte tonal Application No
PCT/IB 99/00892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D271/12 C07D413/12 C07D493/04 A61K31/41 A61K31/44
//(C07D493/04,307:00,307:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GHOSH P B ET AL: "Furazanobenzofuroxan, furazanobenzothiadiazole, and their N-oxides. a new class of vasodilator drugs" JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 2, 1974, pages 203-6, XP002113123 the whole document ---	1-37
X	EP 0 574 726 A (CASSELLA AKTIENGESELLSCHAFT) 22 December 1993 (1993-12-22) the whole document ---	1-37
X	GB 2 029 412 A (CIBA-GEIGY AG) 19 March 1980 (1980-03-19) claim 1 in combination with page 2, lines 27-30 ---	1,2
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	06/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte 'onal Application No
PCT/IB 99/00892

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KATRITZKY A R ET AL: "The proton resonance spectra of heterocycles. Part VII. Substituent effects on coupling constants in bicyclic heteroaromatic compounds and the prediction of chemical shifts from coupling constants" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS II,1972, pages 1682-5, XP002113124 page 1684, table 1, entries 12 and 13, also footnote	1,2
X	GHOSH P B ET AL: "Potential antileukemic and immunosuppressive drugs. Preparation and in vitro pharmacological activity of some benzo-2,1,3-oxadiazoles (benzofurazans) and their N-oxides (benzofuroxans)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 2, 1968, pages 305-11, XP002113125 page 307, table I, entries 28 and 29	1,2,15, 17,32-36
X	BOULTON A J ET AL: "N-oxides and related compounds. Part XXXI. The nuclear magnetic resonance spectra and tautomerism of some substituted benzofuroxans" JOURNAL OF THE CHEMICAL SOCIETY, SECTION B,1967, pages 914-9, XP002113126 page 915, right-hand column, 3rd paragraph	1,2

2

INTERNATIONAL SEARCH REPORT

.rnational application No.
PCT/IB 99/00892

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20-31 and 37
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20-31 and 37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte tional Application No
PCT/IB 99/00892

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 574726 A	22-12-1993	DE 4218977 A	16-12-1993
		CA 2098058 A	11-12-1993
		HU 66084 A	28-09-1994
		JP 6087863 A	29-03-1994
		US 5360812 A	01-11-1994
		ZA 9304024 A	06-01-1994
GB 2029412 A	19-03-1980	US 4185018 A	22-01-1980
		CH 641450 A	29-02-1984